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Analysis of Frusemide by Application of Hydrotropic Solubilization Phenomenon in Solid Dosage Form

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In the present investigation, frusemide has been selected as a poorly water-soluble model drug. There was more than 30-fold enhancement in aqueous solubility of frusemide by 2.0 M sodium salicylate (as compared to aqueous solubility). This hydrotropic agent was employed to solubilize drug from the fine powder of tablet formulations. The hydrotropic agent and the additive used in formulation did not interfere in analysis. Proposed method is new, simple, accurate and reproducible. Statistical data proved the accuracy, reproducibility and the precision of the method.

Key Words: Hydrotropic, Frusemide, Urea, Sodium salicylate.

INTRODUCTION

Increasing aqueous solubility of insoluble and slightly soluble drugs is of major importance. In hydrotropic solubilization phenomenon, addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of urea, nicotinamide, sodium benzoate, sodium salicylate, sodium acetate and sodium citrate ahve been observed to enhance the aqueous solubility of many poorly water-soluble drugs[1-14]. Maheshwari has analyzed various poorly water-soluble drugs *viz.*, cefixime[1], ketoprofen[2,3], salicylic acid[2], tinidazole[4], aceclofenac[5] and amoxicillin[6] using hydrotropy.

There was considerable increase in the solubility of frusemide (a widely used diuretic drug) in 2.0 M sodium salicylate (a hydrotropic soution). Therefore, it was thought worthwhile to solubilize the drug present in its tablet powder with the help of 2.0 M sodium salicylate to carry out its titrimetric analysis.

Various organic solvents like methanol, chloroform, dimethylformamide and ethanol have been used for solubilization of poorly water-soluble drugs to conduct their titrimetric analysis. Drawbacks of organic solvents include their higher costs, toxicities and pollution. The primary goal of

this study was to employ hydrotropic solubilizing agent to exclude the use of an organic solvent, dimethyl formamide. the model drug frusemide (4-chloro-N-furfuryl-5-sulphamoylanthranilic acid) is a widely used diuretic drug.

EXPERIMENTAL

Frusemide was generous gift by Alkem Labs Ltd., Mumbai (India). Commercial tablets of frusemide were procured from the market.

Preliminary solubility studies of drug: Solubility of frusemide was determined at 28 ± 1ºC. An excess amount of drug was added to screw capped 30 mL glass vials containing distilled water and 2.0 M sodium salicylate solution. The vials were shaken mechanically for 12 h and then centrifuged for 5 min at 2000 rpm. The supernatant of each vial was filtered through Whatmann filter paper no. 41. Filtrate was analyzed by titrimetric analysis and necessary correction was made for blank determination.

Analysis of frusemide basic drug sample by the I.P. (1996) method[15]: Accurately weighed (0.5 g) frusemide drug sample was dissolved in 40 mL of dimethyl formamide and titrated with 0.1 N sodium hydroxide solution using bromothymol blue solution as indicator. Blank determination was performed to make necessary correction and drug content was calculated. Titration of this solution was done with 0.1 M sodium hydroxide solution using bromothymol blue solution as indicator. Blank determination was performed to make necessary correction and drug content was calculated (Table-1).

TABLE-1
TITRIMETRIC ANALYSIS DATA OF FRUSEMIDE BULK DRUG

Amount of drug taken (mg)	Amount found (mg)		Percentage estimated	
	I.P.M.	P.M.	I.P.M.	P.M.
500	493.7	502.3	98.74	100.46
500	494.4	496.3	98.88	99.26
500	497.0	498.2	99.40	99.64
500	496.5	494.7	99.30	98.94
500	496.6	496.6	99.32	99.32

I.P.M. = Indian pharmacopoeial Method; P.M. = Proposed method

Analysis of frusemide basic drug sample by the proposed method: Accurately weighed (0.5 g) frusemide drug sample was transferred to a conical flask containing 150 mL of 2.0 M sodium salicylate solution. Flask was shaken for 5 min to solubilize the drug. Solution was titrated with 0.1 M sodium hydroxide solution using phenolphthalein solution as

indicator. Blank determination was done using 150 mL of 2.0 M sodium salicylate solution and after necessary correction, drug content was determined (Table-2).

TABLE-2
STATISTICAL EVALUATION OF ANALYSIS OF FRUSEMIDE BULK DRUG

Method	Mean percentage estimation	Standard deviation	Coefficient of variation (%)	Standard error
I.P.M.	99.13	0.296	0.298	0.148
P.M.	99.52	0.579	0.582	0.290

I.P.M. = Indian pharmacopoeial Method; P.M. = Proposed method

Analysis of frusemide tablet by I.P. (1996) method[16]: 20 Tablets were weighed and powdered. Powder equivalent to about 0.1 g of frusemide was shaken with 150 mL of 0.1 M sodium hydroxide solution and volume was made up to 250 mL with 0.1 M sodium hydroxide and filtered. 5 mL of the filtrate was diluted to 200 mL with 0.1 M sodium hydroxide solution and the absorbance of the resulting solution was measured at 271 nm. The frusemide content was calculated using 580 as the wavelength of (1 %, 1 cm) and the result of analysis are presented in Table-3.

TABLE-3
ANALYSIS DATA OF FRUSEMIDE TABLET FORMULATION WITH STATISTICAL EVALUATION

Tablet formulation	Label claim (mg)	Method	Percentage label claim	Coefficient of variation (%)	Standard error
I	40	I.P.	99.13 ± 0.862	0.870	0.386
	40	P.M.	98.29 ± 1.202	1.223	0.538
II	40	I.P.	99.03 ± 0.621	0.627	0.278
	40	P.M.	98.52 ± 0.962	0.976	0.430

*n = 5

Analysis of frusemide tablets by the proposed method: Tablet powder equivalent to 0.3 g of frusemide was transferred to a conical flask containing 150 mL of 2.0 M sodium salicylate solution. Flask was shaken for about 5 min to solubilize the drug. Titration was done with 0.1 M sodium hydroxide solution using phenolphthalein solution as indicator. Blank determination was performed to make necessary correction and content was calculated (Table-3).

Recovery studies: For recovery studies, 20 and 40 mg of frusemide pure drug were added to tablet powder equivalent to 300 mg frusemide. Procedure of analysis was same using 2.0 M sodium salicylate solution. Per cent recoveries were calculated and reported in Table-4.

TABLE-4
RESULTS OF RECOVERY STUDIES OF TABLET FORMULATION WITH STATISTICAL EVALUATION (FOR PROPOSED METHOD)

Tablet formulation	Amount of drug present in tablet powder taken (mg)	Pure drug added (mg)	Percentage estimated* (mean ± SD)	Coefficient of variation (%)	Standard error
I	300	20	99.03 1.223	1.235	0.547
	300	40	98.77 0.939	0.950	0.420
II	300	20	98.60 1.339	1.358	0.499
	300	40	100.38 1.56	1.558	0.697

RESULTS AND DISCUSSION

Solubility studies indicated that there was more than 30 fold enhancement in solubility of frusemide is 2.0 M sodium salicylate solution as compared to solubility in distilled water. Thus, it was thought worthwhile to employ 2.0 M sodium salicylate solution to solubilizing frusemide to carryout titrimetric analysis excluding the use of costlier organic solvent, dimethyl formamide. Simultaneously, there is no pollution and toxicity.

As evident from Table-1, the result of analysis of frusemide basic drug sample by both pharmacopoeial and proposed method is comparable. This study proves the accuracy of the proposed method. Low values of standard deviation, per cent coefficient of variation and standard error validated the proposed method (Table-2).

Table-3 shows that mean % label claim estimated in two different tablet formulation by I.P. and proposed method are very close to 100 % indicating the accuracy of the proposed method. Accuracy, reproducibility and precision of the proposed method was further confirmed by per cent recovery values in range of 98.60 to 100.38 with satisfactorily low values of standard deviation, % coefficient of variation and standard error (Table-4). The commonly used excipient did not interfere in the proposed analysis.

Conclusion

It was, thus, concluded that the proposed method is new, simple, cost-effective, accurate, safe, free from pollution and precise and can be successfully employed in the routine analysis of frusemide in the basic drugs sample as well as in tablet dosage forms. Just like frusemide (selected as model drug), other poorly water-soluble drugs may be tried to get solubilized by hydrotropic agent to carry out their titrimetric analysis excluding the use of organic solvent.

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